



*Mini review*

## **Acute infection with measles virus predisposes to mastoiditis with concomitant facial paralysis and neck abscess: A minireview of pathomechanism and diagnostic approach**

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**Abstract:** Despite the availability of safe, reliable, and cost-effective measles vaccine, we continue to experience dreadful measles outbreaks with devastating multisystem complications, especially in the pediatric age group. In most instances, the complications arise from a late presentation or delayed institution of appropriate care. With co-existence of measles virus and bacteria in the middle ear, suppurative otitis media can involve the mastoid process and causes fatal complications that manifest late when the patient is in a dire state. This short review highlights the pathogenic mechanisms leading to mastoiditis, facial paralysis, and neck abscess following acute infection with the measles virus, and outlines some useful diagnostic tips. In this review, we searched the international electronic database (PubMed, Web of Science, and Embase) and Google Scholar for articles published on complications of acute measles infection. The keywords used were “mastoiditis”, “mastoid antrum”, “middle ear”, “otitis media”, “Bezold’s abscess”, “facial paralysis” with an operator “OR”; “AND” measles; with restriction to the English language. Also, we searched for similar information in the local clinical and virology journals databases. Thereafter, we reviewed the publications and we described the findings qualitatively.

**Keywords:** Measles; mastoid antrum; middle ear; otitis media; Bezold’s abscess; facial paralysis

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## 1. Introduction

Measles virus (MeV) is the prototype member of the genus Morbillivirus, family Paramyxoviridae, which remains a cause of serious morbidity and mortality in the pediatric age group. Despite global efforts to eliminate MeV, many states in Africa, Europe, and recently some parts of the USA face recurrent outbreaks, with significant loss of lives and devastating sequelae [1–5]. The epidemics occur disproportionately in different parts of the world, aggravated in most endemic regions by the poor standard of living—in some, largely by unimmunized individuals who usually decline vaccination because of medical, religious, and/or philosophic reasons. The death toll of measles epidemics is either under-reported or overflowed. In recent years, several deaths have been reported, indicating that the measles burden is still severe and was attributed to delay in vaccination, suboptimal routine immunization coverage, and wide intervals between follow-ups [2,6]. Another likely problem noted was the use of monovalent measles vaccine as the only available means of preventing the disease in some countries, such as Nigeria, where a single dose is given once, usually at 9 months, for a lifetime.

The existence of simple criteria for a clinical case definition of measles eases the diagnosis by healthcare providers [2], especially in resource-poor settings where simple laboratory confirmatory tests are hard-to-get. Typically, patient with acute suspected measles presents with fever, nasal congestion, cough, conjunctivitis, erythematous maculopapular rash, and pathognomonic Koplik's spot (located on the buccal mucosa). MeV infects multiple organ systems and targets the epithelial and reticuloendothelial system, as well as white blood cells; the infection often leads to profound immune suppression that predisposes the patients to various opportunistic infections, local tissue damages, and a plethora of clinical syndromes [7]. The risk of developing the complications increases with delayed diagnosis, inadequate treatment, and increasing virulence of the pathogen. Simple and cost-effective measures such as vitamin A prophylaxis, adequate hydration, and nutrition, if timely instituted, can minimize the potential complications.

Otitis media is one of the four most frequent complications of measles especially during childhood and accounts for many measles associated hearing loss [8]. Other prominent complications include pneumonia, diarrhea, and encephalitis. Overwhelming immunosuppression provides a suitable environment for bacteria to co-exist in the middle ear, causing a secondary infection. This type of middle ear infection may progress to mastoiditis with concomitant life-threatening extra-cranial or intracranial complications, especially when detected lately or managed poorly [9]. In this minireview, we highlight the clinical anatomy and pathomechanism leading to mastoiditis, facial paralysis, and neck abscess in patients with acute measles virus infection. This information would be helpful to the clinicians to quickly detect and appropriately manage the complication(s) of acute measles virus infection, especially in places where advanced diagnostic facilities are technically unavailable.

## 2. Anatomy

Mastoid bone, a division of the temporal bone, is surrounded by the posterior and middle cranial fossa, the facial canal (*canalis nervi facialis*), sigmoid and lateral sinuses, and the petrous tip of the temporal bone. It develops from a narrow out-pouch of the posterior epitympanum, the "*aditus ad antrum*". The mastoid initially consists of a single cell, known as the antrum, which is linked to the middle ear by a narrow channel. Pneumatization of the antrum begins after birth, shortly after the aerations of the middle ear, and is completed by the age of 10 years. Mastoid air cells are created by

the invasion of epithelium-lined sacs between spicules of the new bone and by the degeneration and re-differentiation of the existing bone marrow spaces. Similar to the mastoid air cells, the antrum is lined with respiratory epithelium that swells in the presence of, and particularly persistent, infection. Because of the proximity of the mastoid to the facial canal, persistent infection can damage the facial nerve and the other anatomically related structures [10]. With persistent otitis media, the inflamed mucosa entraps infection in the air cells by inhibiting drainage and the antrum gets blocked—precluding re-aeration from middle ear—resulting in clinically significant life-threatening complications (Figure 1).

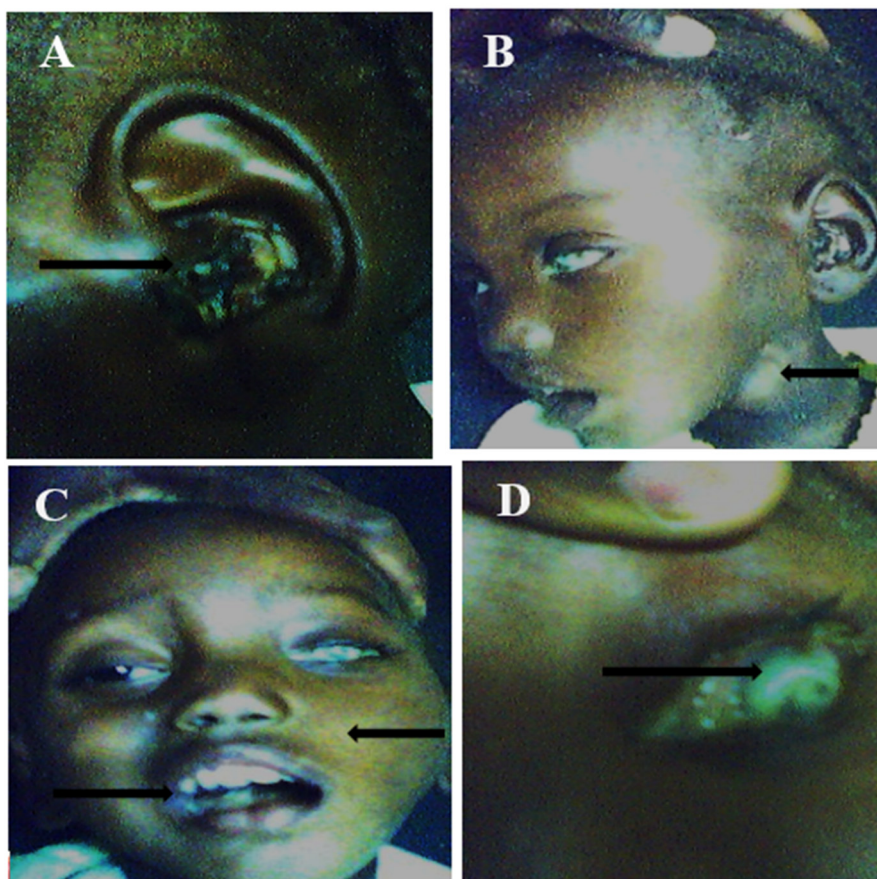
### 3. Clinical scenario

A 2-year old girl with poor immunization history presented with typical features of clinical measles (cough, coryza, and conjunctivitis with diffused maculopapular rashes) for which she was managed as an outpatient in a primary care center. Despite some oral medications (names of which, the parent could not recall), her condition deteriorated with frequent stooling, vomiting, and anorexia. Later she developed a more severe cough, foul-smelling left ear discharge, persistent low-grade fever, weight loss, and deteriorated level of consciousness. The patient was self-referred by her parent to our emergency pediatric unit in the 4<sup>th</sup> week of the illness. On presentation, she was critically ill and was resuscitated accordingly. The pertinent clinical findings were as depicted in the Figure 1 below and she tested seronegative to HIV I & II by a rapid antibody test.

### 4. Pathomechanisms

Measles virus is a highly contagious pathogen with an estimated reproductive number of 12–18. The virus is transmitted via respiratory droplets or aerosols following coughing or sneezing by infected individuals. Virus-containing droplets can remain in the air for several hours and the virus remains infectious on contaminated surfaces for up to two hours. Measles is maximally contagious during the prodromal phase, which lasts 48 hours to 4 days, characterized by intense coughing.

Typically, two important glycoproteins, Fusion (F) and Hemagglutinin (H) play a significant role in measles pathogenesis. However, several immune cell-associated biological molecules, such as the signaling lymphocyte-activation molecule (SLAM), nectin-4 (also known as poliovirus receptor related-4), C-type lectins DC-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), CD46, and Langerin have been described to facilitate the entry and dissemination of the measles virus in both human and animal models [11–14]. SLAM (also known as CDw150) is a special membrane-associated glycoprotein expressed on some immune cells, such as dendritic cells, macrophages, and lymphocytes while nectin-4 is expressed on the basolateral side of polarized epithelial cells, endothelial cells, and keratinocytes. In their recent review, Laksono et al. have described the critical role played by the SLAM and nectin-4 in the current perspective on measles pathogenesis [15–17].



**Figure 1.** Picture of a 2-year old girl showing numerous uncommon complications of measles: (A) Necrosis of surrounding skin and cartilage of the left ear; (B) Left superficial lateral neck abscess, [most likely Bezold's abscess]; (C) A weakness in the left face with a deviation of the angle of the mouth to the right, [left facial paralysis]; and (D) Total opacity and corneal scarring in the left eye.

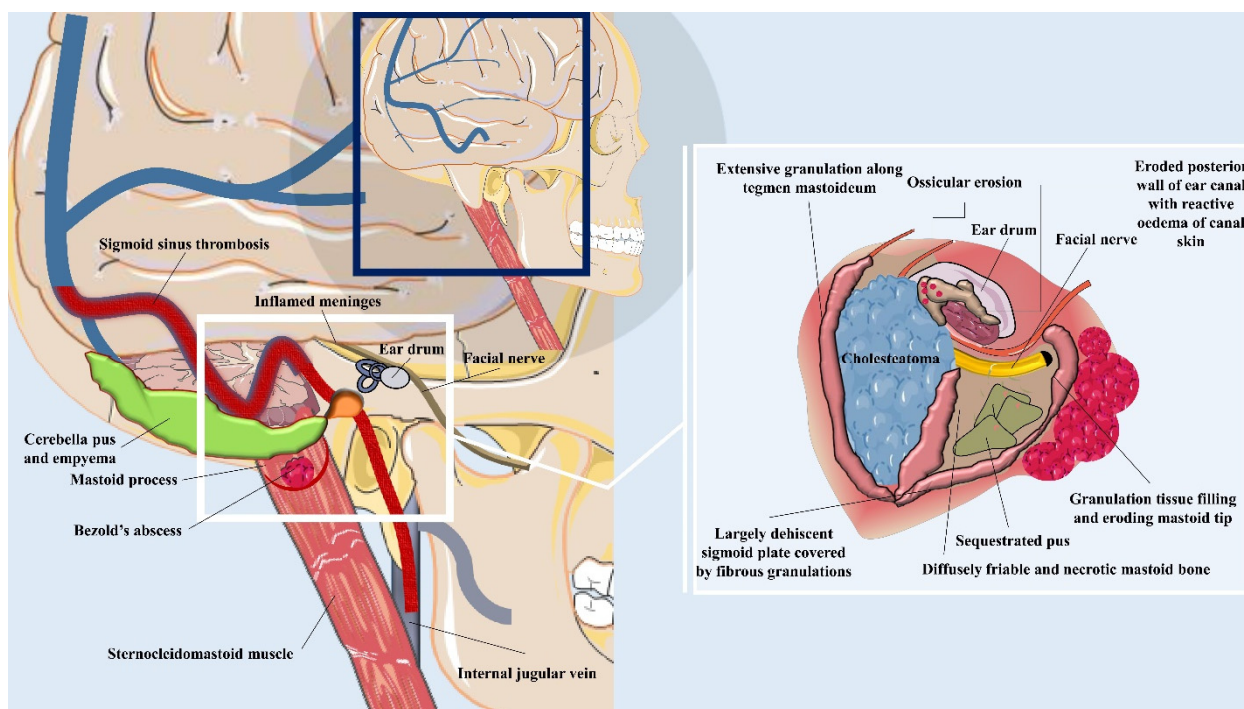
MeV enters and invades the epithelial lining of the upper respiratory tracts and the nasopharynx and then spreads to the regional lymph nodes. It begins by invading the SLAM-positive immune cells, and this brings the virus to local draining lymph nodes. The virus replicates therein and later disseminates to distant reticuloendothelial tissue leading to primary viremia within 2–3 days. Subsequently, intense secondary viremia sets in, which lasts for 4–7 days, characterized by replication in the skin; conjunctivae; respiratory tract; and internal organs, such as the spleen, thymus, lung, liver, and kidneys where further replication continues [18]. During the prodromal phase, the virus can hematogenously circulate back to other organs [17], such as the respiratory tract and intestine, where it now infects nectin-4-positive epithelial cells from their basolateral side. After multiple replications, these cells shed the virus from their apical side into the respiratory tract lumen, from where it is transmitted via aerosols to the next host. The appearance of the skin rash corresponds well with the cytotoxic T lymphocytes attacking measles virus-infected vascular endothelial cells in the skin. Following the appearance of the skin rash, the temperature usually subsides. However, in some individuals, there is persistent hyperthermia with an increased risk of developing complications because of severe immunosuppression and pronounced epithelial tropism. These complications are

more common and intense among malnourished, unvaccinated, vitamin A-deficient children under the age of five years [19].

Numerous complications of otitis media have been described, but their incidences have reduced drastically due to prompt and appropriate selection of antibiotics. However, late detection or poor treatment results in suppuration, persistent inflammation, and accumulation of pus in mastoid air cells [20]. The acute otitis media progresses to acute mastoiditis following a predictive course of events. It starts with hyperemia of the middle ear mucosa and ends with exudate formation in the cavity. At this point, the mastoid cavity fills up with the inflammatory exudate induces periostitis (acute mastoiditis with periostitis), but without bone erosion. The middle ear exudate may become purulent, and perforate the tympanic membrane. With further mucosal inflammation, the aditus and antrum are blocked, causing more fluid accumulation. The inflammatory processes progress and cytokines are released leading to osteoclast activation, decalcification, and bone resorption, thereby creating a coalescent mastoiditis and subperiosteal abscess formation [21]. Progressively, complications may develop at any stage (Figure 2).

Because of the closeness of the mastoid to the facial canal, mastoiditis and mastoid abscess may erode through the antrum and extend to any of the surrounding structures including the facial canal, causing facial nerve palsy—although, the facial nerve is usually well protected in its bony canal. Acute facial nerve palsy likely results from an injury to a dehiscence, exposed facial nerve by bacterial toxin with consequential neural edema. The inflammation and edema compress the nerve trunk inside the fallopian canal, provoking neuropraxia secondary to ischemia [22]. Another theory points towards the demyelination of the facial nerve by toxins produced by the bacteria responsible for the secondary infection. Facial nerve palsy might be the consequence of ischemic phenomena of the vasa nervorum. In all cases, the dehiscence of the fallopian canal in the tympanic cavity facilitates the appearance of peripheral facial paralysis [23]. Besides, facial paralysis can occur weeks after the onset of otitis media, when the bony erosion has occurred to allow access of bacterial toxins to the facial nerve. Bony erosion can also occur in the setting of cholesteatoma that has eroded through the fallopian canal and encroaches the facial nerve directly [24]. Although peripheral facial palsy in the context of simple acute otitis media is very rare because mucoperiosteum is highly resistant to infection, cases have been documented among children between 10 months to 15 years [25].

With a more severe infection of the tip of the mastoid, the suppurative content from the mastoid air cells can descend down the upper insertion of the digastric or sternocleidomastoid muscle to cause pus collection between the muscle and its fascia, leading to various abscesses, like Bezold's abscess, Luc's and Citelli's abscess [26]. Rarely, the pus can descend to the mediastinum and cause acute mediastinitis [27–31]. It is important to note that the presence of thick mastoid bone throughout infancy and early childhood protects against this process [32], and the abscesses are more common in well-pneumatized mastoids than the sclerotic [33]. Moreover, in critical situations where there is negligence, profound immunosuppression, co-existence of the virus and bacteria in the middle ear, delayed diagnosis, and poor response to antibiotics or microbial resistance, we could have a similar or even worse scenario at a young age [27].



**Figure 2.** Illustration of clinical anatomy and pathogenetic mechanism of mastoiditis and facial paralysis following acute measles virus infection.

## 5. Diagnosis

The diagnosis of acute suspected measles is mainly clinical, and the serological test is confirmatory. However, it requires good clinical acumen and reasoning to suspect and diagnose mastoiditis with its resultant complications. In addition to conventional symptoms of measles, and depending on the duration of onset, a patient may present with otalgia, neck swelling, otorrhoea, restricted neck mobility, facial weakness, and hypoacusis. Signs may include post-auricular erythema, with swelling and tenderness; auricular displacement; and cervical tenderness down the sternocleidomastoid muscle; with or without facial nerve palsy. Though other laboratory findings may be nonspecific, culture may yield *Streptococcus pneumoniae* and *Streptococcus pyogenes* [29,34].

Computed tomography (CT) scan and magnetic resonance imaging (MRI) have become the diagnostic tests of choice since they can show involvement of the mastoid process, air-fluid level in the fascial plane, brain abscess, or sinus thrombosis. These techniques would equally help in the determination of the surgical approach to drainage as well as an indication for mastoidectomy and exclusion of other differential diagnoses, such as infective abscesses, lymphadenopathy, and cysts [29,35]. Besides, ultrasonography could also help to differentiate fluid in the soft tissues of the neck from lymphadenopathy [36].

## 6. Summary and conclusion

Acute measles, especially at an early age, is associated with more devastating complications, resulting from the virus itself or secondary bacterial infections leading to local tissue damage and profound cellular immune suppression. Measles-associated otitis media can be complicated by



mastoiditis, facial nerve palsy, meningitis, and brain abscess, however, the presence of thick mastoid bone throughout infancy and early childhood—with the help of potent antibiotics—protects against this process. Since measles is a disease with protean and potentially deceptive complications, proper patient assessment with or without laboratory support and prompt institution of appropriate care would save many lives and reduce morbidity, not underrating the role of immunization, vitamin A supplementation, and adequate proper nutrition.

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### Conflict of interest

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